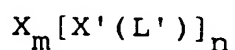


What is claimed:

1. An excipient for a metal chelate contrast agent, wherein said metal chelate contrast agent, $M(L)$, comprises a metal ion complexed with an organic ligand, which excipient has the formula

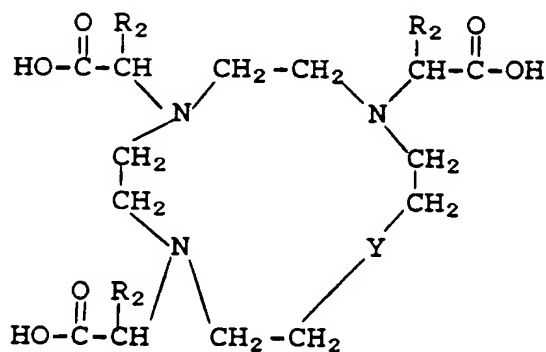


wherein X and X' are each independently selected from calcium or zinc, L' is an organic ligand which may be L or another organic ligand which has a greater affinity for M than for calcium or zinc, and wherein m and n are each independently 1, 2 or 3.

2. The excipient of claim 1 wherein $X = X' = \text{calcium}$.

3. The excipient of claim 1 wherein L and L' are independently selected from linear and macrocyclic polyaminopolycarboxylic acids and derivatives thereof.

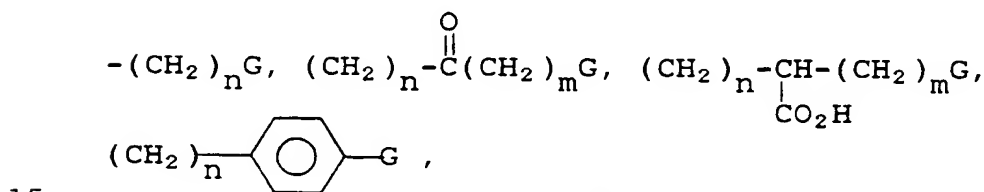
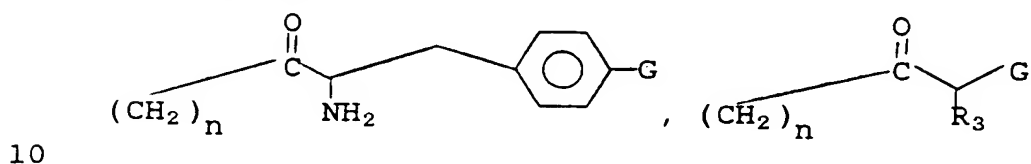
4. The excipient of claim 1 wherein L and L' are independently selected from compounds of the formula



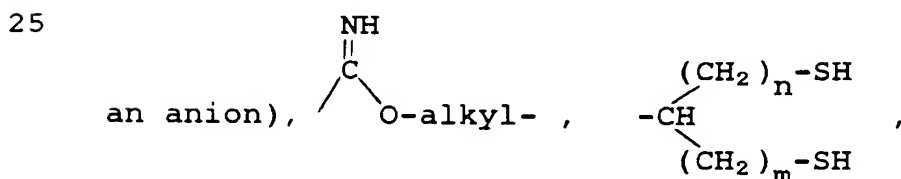
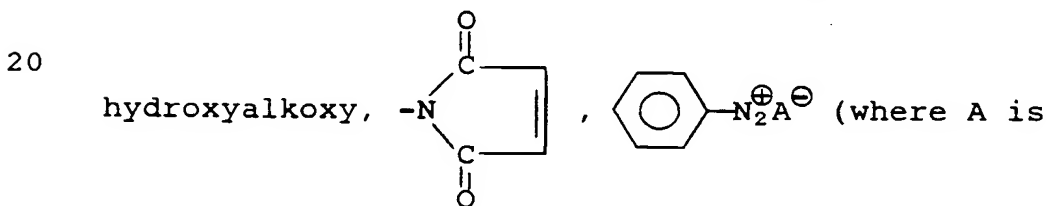
wherein

Y is oxygen or $\overset{\text{R}_1}{\underset{|}{\text{N}}}-$;

R₁ and R₂ are each independently hydrogen,
 5 alkyl, arylalkyl, aryl, alkoxy, hydroxyalkyl,
 hydroxyalkoxy,



wherein G is NH₂, NCS, $\underset{\text{H}}{\underset{|}{\text{N}}} - \overset{\text{O}}{\parallel} \text{C} - \text{CH}_2 - \text{X}$, CO₂H, NHR₄,
 N(R₄)₂, CN, wherein R₄ is alkyl or hydroxyalkyl,



wherein n and m are zero or an integer from one to
 30 five, R₃ is hydrogen, hydroxyalkyl, alkoxy, alkyl,
 aryl, arylalkyl or hydroxyalkoxy and X is chloro,
 bromo or iodo.

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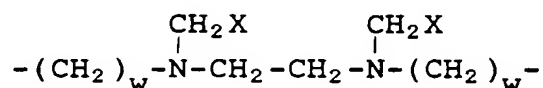


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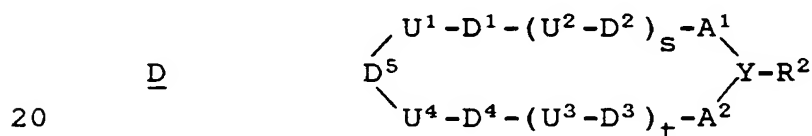
Z is an oxygen atom or a sulfur atom or the group NCH_2X or $\text{NCH}_2\text{CH}_2\text{OR}_4$ wherein X is as defined above and R_4 is C_{1-8} alkyl;

V is X or is $-\text{CH}_2\text{OH}$, $-\text{CONH}(\text{CH}_2)_n\text{X}$ or $-\text{COB}$,
 wherein X is as defined above, B is a protein or
 lipid residue, n is an integer from 1 to 12, or if
 R_1 , R_2 and R_3 are each hydrogen; then both V's
 5 together form the group



10 where X is as above, w is 1, 2 or 3, provided that
 at least two of the substituents Y represent metal
 ion equivalents of an element with an atomic number
 of 21 to 29, 42, 44 or 57 to 83.

6. The excipient of claim 1 wherein L and
 15 L' are independently selected from the compounds of
 the formula



wherein

- Y is N or P;
 A^1 and A^2 are each optionally branched C_{2-6}
 25 alkylene;
 U^1 , U^2 , U^3 and U^4 are each a single bond or
 optionally branched C_{1-6} alkylene;
 D^1 , D^2 , D^3 , D^4 are each O, S, C_{1-6} alkylene
 or NR_7 ;
 30 R_7 is hydrogen or C_{1-4} alkylene having a
 COOR^1 terminal group;
 R^1 is hydrogen or a metal ion equivalent;

D⁵ is D¹ or CHR⁵, where R⁵ can be hydrogen or optionally unsaturated C₁₋₂₀ alkylene which may include imino, phenyleneoxy, phenyleneimino, amido, ester, O, S and/or N optionally substituted with
5 OH, SH imino and/or amino and may carry a terminal functional group (optionally bonded to a macromolecule B);

s and t are each 0-5;

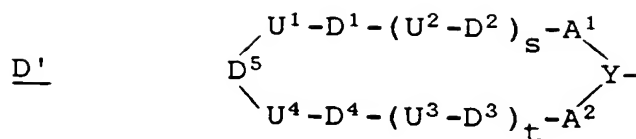
R₂ is hydrogen, optionally substituted C₁₋₁₆
10 alkyl, acyl, acylalkyl (optionally substituted by one or more OH or lower alkoxy groups), -CH₂-X-V, B or CH₂COB where X is CO, optionally branched C₁₋₁₀ alkylene (optionally substituted by 1 or more OH or lower alkoxy groups) or optionally branched C₂₋₂₃
15 alkylene interrupted by O;

V is NR³R⁴ or COOR⁶;

R³ and R⁴ are each hydrogen, C₁₋₁₆ alkyl (optionally substituted by 1 or more OH or lower alkoxy groups) or together complete a 5-6 membered
20 heterocycle optionally containing another heteroatom;

R₆ is hydrogen, C₁₋₁₆ saturated, unsaturated, linear branched or cyclic hydrocarbyl, aryl or aralkyl;

25 R₂ or R₃ can be bonded by a C₂₋₂₀ alkylene chain (optionally having a terminal carbonyl group, optionally interrupted by 1 or more O or R¹ carboxymethylimino, or substituted by one or more OH, lower alkoxy or carboxy lower alkyl groups) to
30 a second macromolecule of the formula



5 which second macromolecule D' can be the same as or different from the macromolecule of D.

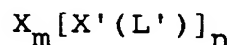
7. The excipient of claim 1 wherein L and L' are independently selected from 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, 1,4,7-tris-(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane,
10 N,N-bis[2-[bis(carboxymethyl)-amino]ethyl]glycine, DTPA-bis methylamide, DTPA bis morpholinoamide and DTPA bis 1,2-dihydroxypropylamide.

15 8. The excipient of claim 1 wherein L and L' are the same organic ligand.

9. A contrast agent composition for use in magnetic resonance, x-ray, ultrasound and radio-diagnostic imaging comprising

20 a metal ion, M, complexed with an organic ligand, L;

a complex salt excipient of the formula



25 wherein X and X' are each independently selected from calcium or zinc, L' is an organic ligand which may be L or another organic ligand which has a greater affinity for M than for calcium or zinc,
30 and wherein m and n are each independently 1, 2 or 3; and,

a pharmaceutically acceptable carrier therefor.

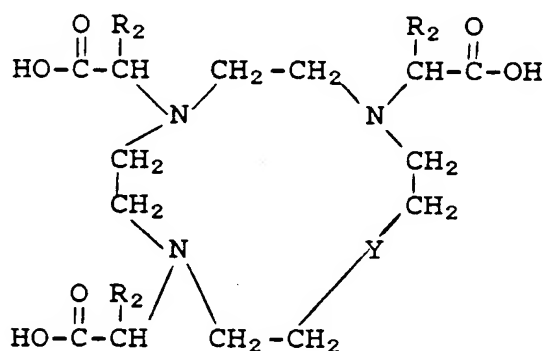
10. The composition of claim 9 where X and X' are each calcium.

11. The composition of claim 9 wherein L and L' are independently selected from linear and
5 macrocyclic polyaminopolycarboxylic acids and derivatives thereof.

12. The composition of claim 9 wherein L and L' are independently selected from compounds of the formula

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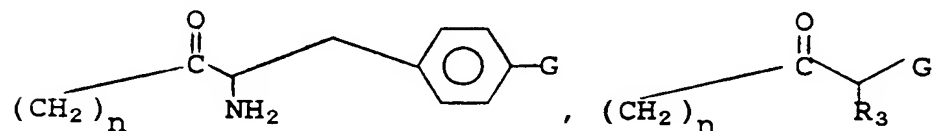
wherein

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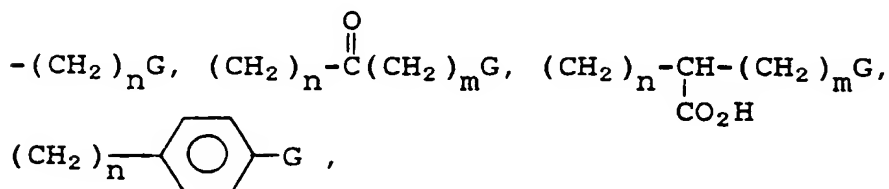
Y is oxygen or $-\overset{\text{R}_1}{\text{N}}-$;

R₁ and R₂ are each independently hydrogen, alkyl, arylalkyl, aryl, alkoxy, hydroxyalkyl, hydroxyalkoxy,

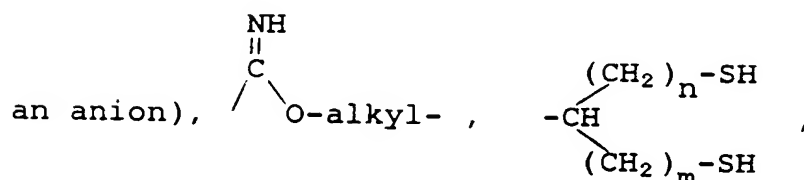
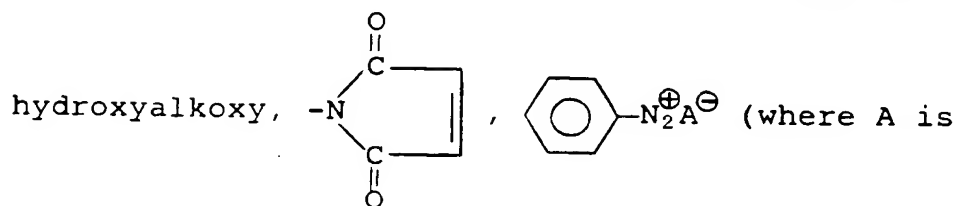
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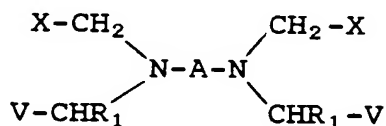


wherein G is NH_2 , NCS , $\text{N}-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-\text{CH}_2-\text{X}$, CO_2H , NHR_4 ,
 $\text{N(R}_4)_2$, CN , wherein R_4 is alkyl or hydroxyalkyl,



wherein n and m are zero or an integer from one to five, R_3 is hydrogen, hydroxyalkyl, alkoxy, alkyl, aryl, arylalkyl or hydroxyalkoxy and X is chloro, bromo or iodo.

13. The composition of claim 9 wherein L and L' are independently selected from the compounds of the formula



or



wherein

X is $-\text{COOY}$, PO_3HY or $-\text{CONHOY}$;

Y is a hydrogen atom, a metal ion equivalent and/or a physiologically biocompatible cation of an inorganic or organic base or amino acid;

A is $-\text{CHR}_2-\text{CHR}_3-$, $-\text{CH}_2\text{CH}_2(\text{ZCH}_2-\text{CH}_2)_m-$,
 5 $-\text{CH}_2-\overset{\text{N}(\text{CH}_2\text{X})_2}{\underset{|}{\text{CH}}}-\text{CH}_2$, or $-\text{CH}_2-\text{CH}_2-\overset{\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_2\text{X})_2}{\underset{|}{\text{N}}}-\text{CH}_2-\text{CH}_2-$, wherein
 X is as defined above;

each R_1 is hydrogen or methyl;

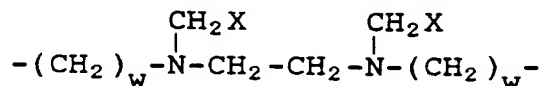
R_2 and R_3 together represent a trimethylene
 10 group or a tetramethylene group or individually are
 hydrogen atoms, lower alkyl groups (e.g., 1-8
 carbons), phenyl groups, benzyl groups or R_2 is a
 hydrogen atom and R_3 is $-(\text{CH}_2)_p-\text{C}_6\text{H}_4-\text{W}-\text{protein}$
 where p is 0 or 1, W is $-\text{NH}-$, $-\text{NHCOCH}_2-$ or $-\text{NHCS}-$,
 15 protein represents a protein residue;

m is 1, 2 or 3;

Z is an oxygen atom or a sulfur atom or the
 group NCH_2X or $\text{NCH}_2\text{CH}_2\text{OR}_4$ wherein X is as defined
 above and R_4 is C_{1-8} alkyl;

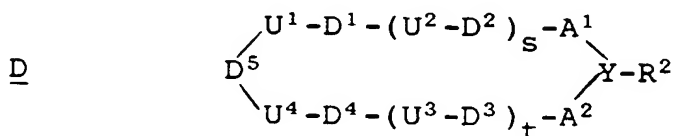
20 V is X or is $-\text{CH}_2\text{OH}$, $-\text{CONH}(\text{CH}_2)_n\text{X}$ or $-\text{COB}$,
 wherein X is as defined above, B is a protein or
 lipid residue, n is an integer from 1 to 12, or if
 R_1 , R_2 and R_3 are each hydrogen; then both V's
 together form the group

25



where X is as above, w is 1, 2 or 3, provided that
 30 at least two of the substituents Y represent metal
 ion equivalents of an element with an atomic number
 of 21 to 29, 42, 44 or 57 to 83.

5



10

A^1 and A^2 are each optionally branched C_{2-6} ne;

U¹, U², U³ and U⁴ are each a single bond or optionally branched C₁₋₆ alkylene;

15

D¹, D², D³, D⁴ are each O, S, C₁₋₆ alkylene or NR₇;

R₇ is hydrogen or C₁₋₄ alkylene having a COOR¹ terminal group;

R¹ is hydrogen or a metal ion equivalent;

20

D⁵ is D¹ or CHR⁵, where R⁵ can be hydrogen or optionally unsaturated C₁₋₂₀ alkylene which may include imino, phenyleneoxy, phenyleneimino, amido, ester, O, S and/or N optionally substituted with OH, SH imino and/or amino and may carry a terminal functional group (optionally bonded to a macromolecule B);

s and t are each 0-5;

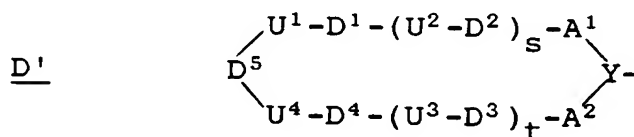
R₂ is hydrogen, optionally substituted C₁₋₁₆ alkyl, acyl, acylalkyl (optionally substituted by one or more OH or lower alkoxy groups), -CH₂-X-V, B or CH₂COB where X is CO, optionally branched C₁₋₁₀ alkylene (optionally substituted by 1 or more OH or lower alkoxy groups) or optionally branched C₂₋₂₃ alkylene interrupted by O;

V is NR^3R^4 or COOR^6 ;

R^3 and R^4 are each hydrogen, C_{1-16} alkyl (optionally substituted by 1 or more OH or lower alkoxy groups) or together complete a 5-6 membered heterocycle optionally containing another heteroatom;

R_6 is hydrogen, C_{1-16} saturated, unsaturated, linear branched or cyclic hydrocarbyl, aryl or aralkyl;

R_2 or R_3 can be bonded by a C_{2-20} alkylene chain (optionally having a terminal carbonyl group, optionally interrupted by 1 or more O or R^1 carboxymethylimino, or substituted by one or more OH, lower alkoxy or carboxy lower alkyl groups) to a second macromolecule of the formula



which second macromolecule D' can be the same as or different from the macromolecule of D.

15. The composition of claim 9 wherein L and L' are independently selected from 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane, N,N-bis[2-[bis(carboxymethyl)-amino]ethyl]glycine, DTPA bis methylamide, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DTPA bis morpholinoamide and DTPA bis 1,2-dihydroxypropylamide.

16. The composition of claim 9 wherein L and L' are the same organic ligand.

17. The composition of claim 9 wherein the mole ratio of said complex salt to said metal
5 chelate contrast agent is between about 0.05 and 10 percent.

18. The composition of claim 9 wherein said metal ion is selected from paramagnetic metal atoms, lanthanide series elements, yttrium, and the
10 transition series elements.

19. The composition of claim 18 wherein said paramagnetic metals are selected from gadolinium(III), dysprosium(III), manganese(II), manganese(III), chromium(III), iron(II) and iron(III).

20. The composition of claim 9 wherein said
15 metal ion complexed with an organic ligand is gadolinium(III) 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane and said excipient is calcium bis[1,4,7-tris(carboxy-
20 methyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecanatocalcium(II)].

21. The composition of claim 9 wherein said metal ion complexed with an organic ligand is N-methylglucamine gadolinium (III) 1,4,7,10-tetra-
25 azacyclododecane-N,N',N'',N'''-tetraacetic acid and said excipient is calcium [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetatocalcium(II)].

22. The composition of claim 9 wherein said metal ion complexed with an organic ligand is di-
30 N-methylglucaminium gadolinium(III) N,N-bis[2-[bis(carboxymethyl)-amino]ethyl]glycine and said excipient is calcium bis[diethylenetriamine-N,N',N',N'',N'''-pentaacetatocalcium(II)].

23. The composition of claim 9 wherein said metal ion complexed with an organic ligand is diethylene triamine pentaacetato-bis methyllamde-gadolinium(III) and said excipient is calcium
5 bis[diethylenetriamine-N,N'N',N'',N''-pentaacetato-bis methyllamde-calcium(II)].

24. The composition of claim 9 wherein said metal ion complexed with an organic ligand is gadolinium(III) 1,4,7,10-tetraazacyclododecane-
10 1,4,7-triacetic acid and said excipient is calcium bis[1,4,7,10-tetraazacyclododecane-1,4,7-triaceta-tocalcium(II)].

25. The composition of claim 9 wherein said metal ion complexed with an organic ligand is
15 gadolinium (III) DTPA bis morpholinoamide and said excipient is calcium bis [DTPA-bis morpholinamido calcium (II)].

26. The composition of claim 9 wherein said metal ion complexed with an organic ligand is
20 gadolinium (III) DTPA bis 1,2-dihydroxypropylamide and said excipient is calcium bis[DTPA bis 1,2-dihydroxypropylamido calcium (II)].

27. A contrast agent composition comprising a metal chelate which is gadolinium (III)
25 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane;

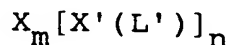
an excipient which is calcium bis[1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecanatocalcium(II)];

30 a buffer;

acidic and/or basic solution sufficient to adjust pH of said composition to a desired value; and

water.

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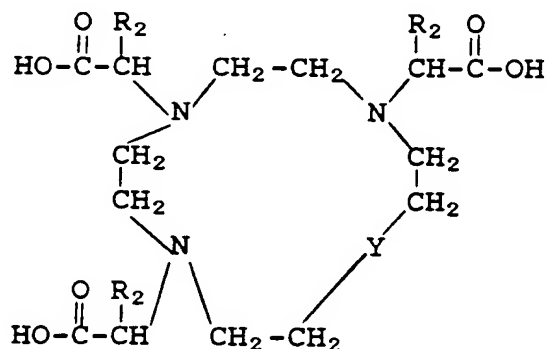


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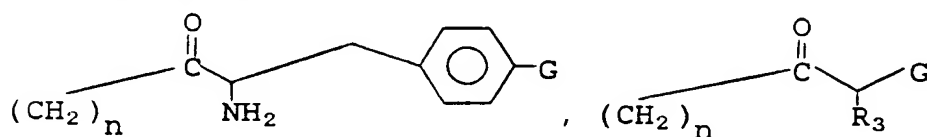
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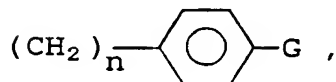
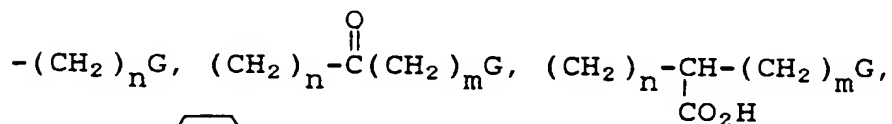
wherein

Y is oxygen or $\overset{\text{R}_1}{\underset{|}{\text{N}}}$;

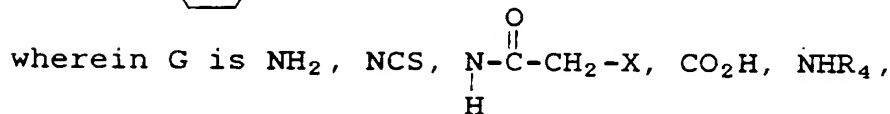
R₁ and R₂ are each independently hydrogen,
 5 alkyl, arylalkyl, aryl, alkoxy, hydroxyalkyl,
 hydroxyalkoxy,



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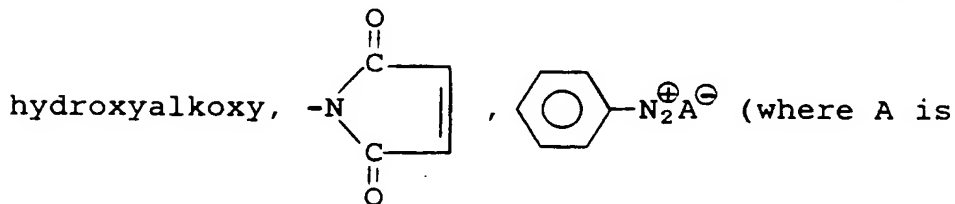


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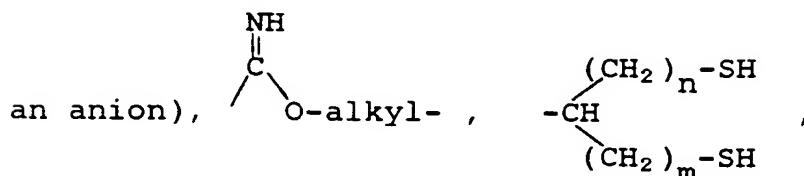


N(R₄)₂, CN, wherein R₄ is alkyl or hydroxyalkyl,

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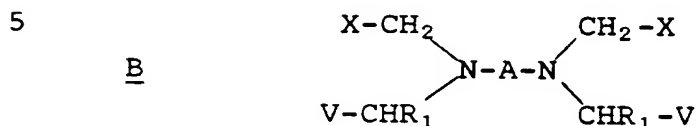


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wherein n and m are zero or an integer from one to
 30 five, R₃ is hydrogen, hydroxyalkyl, alkoxy, alkyl,
 aryl, arylalkyl or hydroxyalkoxy and X is chloro,
 bromo or iodo.

32. The method of claim 28 wherein L and L' are independently selected from the compounds of the formula



or



wherein

X is -COOY, PO₃HY or -CONHOY;

15 Y is a hydrogen atom, a metal ion equivalent and/or a physiologically biocompatible cation of an inorganic or organic base or amino acid;

A is -CHR₂-CHR₃-, -CH₂CH₂(ZCH₂-CH₂)_m-,

20 $\begin{array}{c} \text{N}(\text{CH}_2\text{X})_2 \\ | \\ -\text{CH}_2-\text{CH}-\text{CH}_2 \end{array}$, or $\begin{array}{c} \text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_2\text{X})_2 \\ | \\ -\text{CH}_2-\text{CH}_2-\text{N}-\text{CH}_2-\text{CH}_2- \end{array}$, wherein X is as defined above;

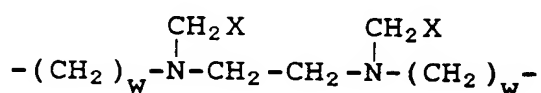
each R₁ is hydrogen or methyl;

R₂ and R₃ together represent a trimethylene group or a tetramethylene group or individually are hydrogen atoms, lower alkyl groups (e.g., 1-8 carbons), phenyl groups, benzyl groups or R₂ is a hydrogen atom and R₃ is -(CH₂)_p-C₆H₄-W-protein where p is 0 or 1, W is -NH-, -NHCOCH₂- or -NHCS-, protein represents a protein residue;

30 m is 1, 2 or 3;

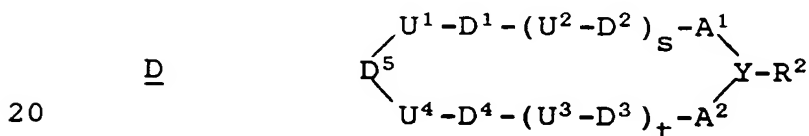
Z is an oxygen atom or a sulfur atom or the group NCH₂X or NCH₂CH₂OR₄ wherein X is as defined above and R₄ is C₁₋₈alkyl;

V is X or is $-\text{CH}_2\text{OH}$, $-\text{CONH}(\text{CH}_2)_n\text{X}$ or $-\text{COB}$,
 wherein X is as defined above, B is a protein or
 lipid residue, n is an integer from 1 to 12, or if
 R_1 , R_2 and R_3 are each hydrogen; then both V's
 5 together form the group



10 where X is as above, w is 1, 2 or 3, provided that
 at least two of the substituents Y represent metal
 ion equivalents of an element with an atomic number
 of 21 to 29, 42, 44 or 57 to 83.

33. The method of claim 28 wherein L and L'
 15 are independently selected from the compounds of
 the formula



wherein

Y is N or P;

25 A^1 and A^2 are each optionally branched C_{2-6}
 alkylene;

U^1 , U^2 , U^3 and U^4 are each a single bond or
 optionally branched C_{1-6} alkylene;

D^1 , D^2 , D^3 , D^4 are each O, S, C_{1-6} alkylene
 or NR_7 ;

30 R_7 is hydrogen or C_{1-4} alkylene having a
 COOR^1 terminal group;

R^1 is hydrogen or a metal ion equivalent;

D⁵ is D¹ or CHR⁵, where R⁵ can be hydrogen or optionally unsaturated C₁₋₂₀ alkylene which may include imino, phenyleneoxy, phenyleneimino, amido, ester, O, S and/or N optionally substituted with
5 OH, SH imino and/or amino and may carry a terminal functional group (optionally bonded to a macromolecule B);

s and t are each 0-5;

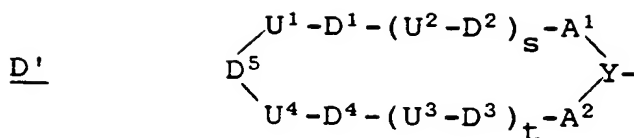
R₂ is hydrogen, optionally substituted C₁₋₁₆
10 alkyl, acyl, acylalkyl (optionally substituted by one or more OH or lower alkoxy groups), -CH₂-X-V, B or CH₂COB where X is CO, optionally branched C₁₋₁₀ alkylene (optionally substituted by 1 or more OH or lower alkoxy groups) or optionally branched C₂₋₂₃
15 alkylene interrupted by O;

V is NR³R⁴ or COOR⁶;

R³ and R⁴ are each hydrogen, C₁₋₁₆ alkyl (optionally substituted by 1 or more OH or lower alkoxy groups) or together complete a 5-6 membered
20 heterocycle optionally containing another heteroatom;

R₆ is hydrogen, C₁₋₁₆ saturated, unsaturated, linear branched or cyclic hydrocarbyl, aryl or aralkyl;

25 R₂ or R₃ can be bonded by a C₂₋₂₀ alkylene chain (optionally having a terminal carbonyl group, optionally interrupted by 1 or more O or R¹ carboxymethylimino, or substituted by one or more OH, lower alkoxy or carboxy lower alkyl groups) to
30 a second macromolecule of the formula



5 which second macromolecule D' can be the same as or different from the macromolecule of D.

34. The method of claim 28 wherein L and L' are independently selected from 1,4,7,10-tetra-
azacyclododecane-1,4,7-triacetic acid, 1,4,7-tris-
10 (carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-
tetraazacyclododecane, N,N-bis[2-[bis(carboxy-
methyl)-amino]ethyl]glycine, DTPA-bis methyllamide,
1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic
acid, DTPA bis morpholinoamide and DTPA bis 1,2-
15 dihydroxypropylamide.

35. The method of claim 28 wherein L and L' are the same organic ligand.

36. The method of claim 28 wherein the mole
ratio of said complex salt to said metal chelate
20 contrast agent is between about 0.05 and 10
percent.

37. The method of claim 28 wherein said
metal ion is selected from paramagnetic metal
atoms, lanthanide series elements, yttrium, and the
25 transition series elements.

38. The method of claim 28 wherein said
paramagnetic metals are selected from gadolinium
(III), octahedral manganese(II), chromium(III), and
iron(III).

39. The method of claim 28 wherein said metal ion complexed with an organic ligand is gadolinium(III) 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane and
5 said excipient is calcium bis[1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecanatocalcium(II)].

40. The method of claim 28 wherein said metal ion complexed with an organic ligand is
10 N-methylglucamine gadolinium (III) 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid and said excipient is calcium [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetatocalcium(II)].

41. The method of claim 28 wherein said
15 metal ion complexed with an organic ligand is di-Nmethylglucamine gadolinium(III) N,N-bis[2-[bis(carboxymethyl)-amino]ethyl]glycine and said excipient is calcium bis[diethylenetriamine-N,N',N',N'',N''-pentaacetatocalcium(II)].

20 42. The method of claim 28 wherein said metal ion complexed with an organic ligand is gadolinium(III) N,N-bis[2-[bis(carboxymethyl)-amino]ethyl]glycine-bis methylamide and said excipient is calcium bis[diethylenetriamine-
25 N,N',N',N'',N''-pentaacetato-bis methylamide-calcium(II)].

43. The method of claim 28 wherein said metal ion complexed with an organic ligand is gadolinium(III) 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid and said excipient is calcium bis[1,4,7,10-tetraazacyclododecane-1,4,7-triacetatocalcium(II)].

44. The method of claim 28 wherein said metal ion complexed with an organic ligand is gadolinium (III) DTPA bis morpholinoamide and said excipient is calcium bis [DTPA-bis morpholinamido calcium (II)].

45. The method of claim 28 wherein said metal ion complexed with an organic ligand is gadolinium (III) DTPA bis 1,2-dihydroxypropylamide and said excipient is calcium bis[DTPA bis 1,2-dihydroxypropylamido calcium (II)].

46. The method of claim 28 wherein said contrast agent composition comprising
a metal chelate which is gadolinium (III)
1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-
1,4,7,10-tetraazacyclododecane;
an excipient which is calcium bis[1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecanatocalcium(II)];
a buffer;
acidic and/or basic solution sufficient to adjust pH of said composition to a desired value;
and
water.